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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,243	01/04/2002	Paul I. Freimuth	BSA 01-22	6646

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/037,243	FREIMUTH ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64, 93, 95-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,93 and 95-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/6/2006 has been entered.

Claims 64, 95 and 97-98 have been amended, and claims 1-63, 87-92 and 94 are canceled in the amendment filed 11/6/2006.

Claims 64, 93 and 95-98 are under examination.

Claim Objections

Claims 63, 88, 89 and 91 have been cancelled, therefore the objection to claims 63, 88, 89 and 91 under 37 CFR 1.75(c) is moot.

Claim Rejections - 35 USC § 102

Claims 53, 63, 88-91 and 94 have been cancelled, therefore their rejections under 35 U.S.C. § 102(b) are moot. Claim 95 has been amended to depend from claim 64 and claim 96 is dependent on claim 95. The rejection of claims 95-96 under 35 U.S.C. § 102(b) is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53, 63, 87-91 and 94 have been cancelled, rendering their rejections under 35 USC § 112, second paragraph moot. Claim 95 has been amended to depend from claim 64.

Claims 64, 93 and 95-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64 and 93 are vague and indefinite because they recite the phrase, "the expression vector further comprising a multiple cloning site for inserting, in-frame with said first nucleic acid sequence, a second nucleic acid sequence encoding a protein or polypeptide of interest" and as written, it is not clear what is comprised in the expression vector.

It is not clear whether the second nucleic acid sequence is actually present in the claimed expression vector because the claim recites "further comprising a multiple cloning site for inserting" the second nucleic acid sequence but does not appear to recite that the vector comprises the second sequence, only that the multiple cloning site is present. Also, it is not clear what element the phrase "in-frame with said first nucleic acid sequence" is intended to limit. As written, it is not clear if Applicants intend the multiple cloning site to be in-frame with the first nucleic acid sequence or whether the

second nucleic acid sequence is intended to be in-frame with the first nucleic acid sequence.

Claims 95-98 are indefinite insofar as they are dependent on indefinite claims. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53, 63, 87-92 and 94 have been cancelled; therefore their rejections under 35 USC § 112, first paragraph are moot.

Claims 64, 93 and 95-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 64 is newly added to this rejection.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 5/5/2006 and for reasons outlined below.

Applicants submit that claim 93 as previously amended and re-presented here, is fully supported by the written description with respect to the peptide extensions as the claimed peptide extensions were described in detail as itemized in Table I of the Specification. Applicants submit that the language "comprises the carboxyl- terminal 57 amino acids of the T7 gene 10B protein" was not contained in this claim as originally presented and therefore it is the Applicants' position that this basis for rejection of Claim

93 is unfounded. Applicants submit that that "consisting essentially of the encoded peptide fused to the carboxy(l)-terminus of the protein polypeptide of interest" is well understood by those of skill in the art and is fully supported by the written description of the specification.

Applicants submit that while the Examiner further indicates that the written description does not support a vector optimized for use in "all protozoans", a person of skill in the art would "conclude that the vector is optimized for use in certain bacterial cells". The Applicants submit that those of skill in the art are familiar with the various expression vectors that have been optimized for use in various bacterial cells. Applicants further submit that the skilled artisan would find it a simple matter to choose a vector optimized for his/her 'bacterial cells of choice' and would be extremely unlikely to choose a vector optimized for use in one host in a different host. Applicants submit that in any system for expression of proteins or polypeptides of interest, vectors optimized for use in particular host cells can be created so that the peptide extensions are encoded in frame with the protein or polypeptide of interest so that the expressed fusion protein includes the peptide extension fused to the carboxyl-terminus of the protein or polypeptide of interest. Applicants submit that if a person of skill in the art developed a vector for use in an extreme halophile (to use the Examiner's example), it would be a simple matter for such person to incorporate the coding sequences for the peptide extensions into vector. Applicants submit that, expression vectors optimized for use bacterial cells is enabled by the written description since it is only a matter of selection by the person of skill in the art as to which expression host he or she will use.

Applicant's arguments filed 11/6/2006 have been fully considered but they are not persuasive. The claimed expression vector encompasses an extremely large genus of vectors that would include the limitation of comprising SEQ ID NO:6 (Peptide T7B) operably linked to a sequence encoding a protein of interest and a multiple cloning site. The genus would include any expression vector comprising these limitations and that could be optimized in any manner for use in any type of bacterial cell. The genus further includes any sequence including a polypeptide of interest, which is a very large number of polypeptides or proteins, since the disclosure does not specify or limit to who the proteins would be of interest or would require enhanced solubility or folding. Using the broadest reasonable interpretation, the genus encompasses any expression vector useful in any type of bacteria and that comprises a sequence encoding any possible protein of interest that could be expressed from a vector, as long as the sequence can be inserted in frame at a MCS and be expressed as a fusion protein with Peptide T7B.

In the specification, there is no description of any other expression vector besides pET15b- CAR D1 that would be optimized for expression in any other bacteria besides *E.coli* and that would express any polypeptide of interest. There is no description of how the structure of the disclosed expression vectors relates to the structure any of the other expression vectors in the claimed genus. The applicant does not provide an indication of how the sequence of the exemplified expression vectors are representative of other expression vectors for use in any other bacterial cell besides *E.coli* to express any other polypeptide of interest linked to a peptide T7B extension. The common attributes of any other optimized expression vector are not described and

the identifying attributes of the individual optimized expression vectors comprising any other polypeptide of interest to the disclosed expression vectors are not described.

Response to Arguments

Claim 93 is limited to the described peptide extension, and herein to the elected species of Peptide T7B, but the inclusion of claim 93 and dependent claims 97-98 in this rejection is not unfounded. The basis for this rejection lies in the description of the entire expression vector as claimed.

Applicants submit that the limitation of "consisting essentially " is well understood by skilled artisan. However, the phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. As the claim is written, the limitation of the fusion protein "consists essentially of" the encoded protein extension fused to the carboxyl-terminus of the protein of interest. As long as the expression vector encodes a sequence that produces a peptide extension fused to the C-terminus of the protein of interest (i.e. the basic and novel characteristic(s) of the claimed invention), any other elements that do not materially affect this characteristic can be present on the expression vector. Therefore the claim encompasses a large genus of vectors comprising multiple and varied elements. Applicant is invited to review MPEP 2105:

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original) ..... "A consisting

essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir.1998). See also *Atlas Powder v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *In re Janakirama-Rao*, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); *Water Technologies Corp. vs. Calco, Ltd.*, 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., *PPG,* 156 F.3d at 1355, 48 USPQ2d at 1355.

Applicants claim an expression vector optimized for use in bacterial cells comprising a first nucleic acid sequence encoding a peptide extension wherein the encoded peptide is elected SEQ ID NO:6 (Peptide T7B), the expression vector further comprising a multiple cloning site for inserting in frame with said first nucleic acid sequence, a second nucleic acid sequence encoding a protein or polypeptide of interest, wherein expression of the nucleic acid sequences yields a fusion protein consisting essentially of the encoded peptide extension fused to the Carboxy terminus of the protein or polypeptide of interest. As written, claim 64 does not recite a function for the peptide extension to be expressed with the claimed expression vector other than "for use in bacterial cells". Claim 93 recites that the expression vector is "for enhancing the solubility and proper folding of an expressed protein or polypeptide of interest". It appears that the intended use of the vector of claim 64 is also for enhancing the solubility and proper folding of an expressed protein or polypeptide of interest.

The satisfaction of the written description requirement is not based on what a skilled artisan would conclude about the claimed invention, but rather on the disclosure of the invention to describe the structure of the claimed invention as Applicants intend.

There are various expression vectors that are optimized for use in certain bacterial cells that are commercially available. However, these vectors are not sufficiently described in the specification. Further, as the invention is claimed, it encompasses a very large genus of expression vectors that have not been sufficiently described so that the skilled artisan would know that they would perform the claimed function. The disclosure does not specify any other bacterial cell hosts beyond the claimed bacterial cells, and does not describe in what way a vector would be optimized for any bacterial cell of choice.

Applicants submit that vectors optimized for use in particular host cells can be created and it would be a simple matter for the skilled artisan to develop a vector as claimed for use even in an extreme halophile. However, the instant disclosure has not provided any description of the structure of such vectors optimized for any other expression vector besides the exemplified vectors. The skilled artisan would not know what the Applicants intend as the structure of an expression vector comprising a peptide T7B linked to a polypeptide of choice, and optimized as claimed for an extreme halophile or any popular host of choice, so that it would have the function of enhancing the solubility and folding of the polypeptide of interest, because such structures have not been adequately described in the specification. According to these facts, one of skill in the art would conclude that Applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variant of the genus and is insufficient to support them.

Claims 64, 93 and 95-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification; while being enabling for a nucleic acid encoding aT7B peptide linked to the carboxy terminal of a protein of interest under physiological conditions and enhancing the protein's solubility and proper folding in *E. coli*, does not reasonably provide enablement for any peptide extension of 1 to 61 amino acids linked to any target protein to enhance protein folding and solubility when expressed in any bacterial host cell. Claims 53, 63, 87-92 and 94 have been cancelled; therefore their rejections under 35 USC § 112, first paragraph are moot.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 5/5/2006 and for reasons outlined below.

Applicants request reconsideration and withdraw of this rejection. With respect to the Examiner's remarks on the breadth of the expression "consisting essentially of":

> "information is not provided for the limitation of the nucleic acid sequences consisting essentially of the encoded peptide fused to the carboxy- terminus of the protein of interest. As "consisting essentially of" may be broadly interpreted to mean the encoded peptide fused to the protein of interest plus any conceivable possible sequence, then the peptide fusion may include the T7B peptide, the protein of interest [and] any other possible sequence without limitation",

Applicants respectfully submit that a person of skill in the art would find it extremely unreasonable to include "any other possible sequence without limitation" in a construct designed to express a protein or polypeptide of interest. Applicants submit that a skilled artisan would know that doing so would be counterproductive to the goal of expressing the protein or polypeptide of interest in a soluble, correctly folded state. Applicants submit that persons of skill in the art readily recognize that "consisting essentially of" means, for example, the protein or polypeptide of interest, the carboxyl-

terminal peptide extension and additional amino acids such as encoded amino acids which may be later cleaved from the expressed protein during processing by the host cell - e.g. during transport to the bacterial periplasm or transport to the medium in the case of proteins that are extruded from the cell or any few encoded amino acids that could not be eliminated from the cloned coding sequence because of cloning difficulties related to lack of restriction sites, etc. Applicants submit that in the present instance, for example, this would encompass the amino acids Lys - Glu - Asp - Pro (LEDP) that are at the N-terminus of each of the encoded peptide extensions of Table I and the claims.

Applicant's arguments filed 11/6/2006 have been fully considered but they are not persuasive. An enabling disclosure must be sufficient so that skilled artisan is able to make and use the claimed invention without excessive trial and error experimentation. The argument regarding the phrase "consisting essentially of" has been addressed in the above rejection. Specific to this lack of enablement rejection, the disclosure has not provide sufficient guidance on how to make the large genus of claimed expression vectors consisting essentially of the claimed limitations of a sequence that produces a peptide extension fused to the C-terminus of the protein of interest (i.e. the basic and novel characteristic(s) of the claimed invention), with any other elements that do not materially effect this characteristic. The skilled artisan would not know what sequences encoding amino acids such as suggested above could be included in the claimed expression vectors so that that the solubility and folding of *any* encoded protein would be enhanced without a great deal of trial and error experimentation.

Therefore the claimed invention encompasses a large genus of vectors comprising a genus of multiple elements, including a sequence encoding any of a large number of proteins of interest which would have various solubilities and folding characteristics from each other and also according to the host cell type. The inventive expression vectors are optimized for any bacterial cell type and can contain elements that do not materially affect the basic and novel characteristic(s) of the vector. Due to the scope of the claims, the state and unpredictability of the art, as well as the examples and guidance provided by the instant specification, the skilled artisan would have to use excessive experimentation to empirically determine how to make and use the claimed expression vectors.

As *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), the skilled artisan might eventually find out how to use the invention after "a great deal of work". In the case of *In re Gardner, Roe and Willey*, the invention was a compound which the inventor claimed to have antidepressant activity, but was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclosure of effective drug dosage. The court held that "the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves".

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
Examiner
1/12/2007

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PRIMARY EXAMINER